Revocation and Substitute Power, **please direct all future correspondence regarding the subject application to CUSTOMER NUMBER 22798, that is:**

22798

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Substitute Declaration.

Applicants note that the Examiner alleged that the present Oath/Declaration is defective and requested a substitute Oath/Declaration. Per the Examiner's request, Applicants are presently obtaining a substitute declaration and will provide such when the document is executed.

35 U.S.C. §112, First Paragraph.

The rejection of claims 3-13, 26-22, 34-44, and 53-54 under 35 U.S.C. §112, first paragraph, was maintained. In particular, the Examiner alleged that Applicants have not demonstrated "how to use" the proteins (single chain antibodies) recited in claims 3-13, 16-22, and 53-54. In particular the Examiner alleged that it is unclear that antibodies that meet the limitations of these claims would bind antigen as claimed. More specifically, the Examiner alleged that:

1) "It is unclear than an antibody that contains one, two, or three CDR would bind antigen as claimed" (office Action, page 3)

2) "The specification "does not enable the myriad of antibodies encompassed by claim 4 which recites an antibody that is 70% sequence identity with SQ ID NO:1 or 2 that would bind to the c-erbB2 on cells with an affinity of at least 10 mM. (Office Action, pages 3-4).

3_ It is not clear if an antibody that comprises at least 10 contiguous amino acids (which can be framework residues) from the polypeptide as set forth in SEQ ID NO:1 or 2 would bind specifically to the c-erbB2 receptor as claimed in claim 16" (Office Action, page 4).

Applicants respectfully traverse. In making his rejection under 35 U.S.C. §112, first paragraph, the Examiner improperly ignores limitations of the recited claims. In particular, the base claim (claim 10) expressly recites:

> 1. A single chain antibody that **specifically binds to a c-erbB2 receptor**, wherein said antibody **specifically binds to an epitope bound by F5 (SEQ ID NO:1) or C1** (SEQ ID NO:2), and further **wherein said antibody is an internalizing antibody**.

If an antibody does not specifically bind to a c-erbB2 receptor at the recited epitope or is not an internalizing antibody, then such antibody is not within the literal scope of the claimed invention (*i.e.,* in effect the claims expressly exclude inoperable embodiments). **In other words, Applicants claims only literally read on antibodies that specifically bind to the c-erbB2 receptor as indicated, and Applicants have clearly taught "how to use" such antibodies.**

Moreover, the Examiner is also reminded that a claim need not exclude possible inoperable embodiments. As stated by the PTO Board of Appeals:

> It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination. *Ex parte* Cole, 223 USPQ 94 (BPAI 1983)

Similarly, the Federal Circuit has stated that

> It is not the function of claims to specifically exclude either possible inoperative substances or ineffective reactant proportions. *In re Dinh-Nguyen and Stenhagen*, 181 USPQ 46 (CCPA 1974)

For a proposed claim to be unpatentable, the law requires that the number of inoperable embodiments be significant in numbers **and not readily ascertained** by those of skill. *In re Cook and Merigold*, 169 USPQ 298, 301-302 (CCPA, 1971).

In the present case **inoperable embodiments are readily ascertained** by one of ordinary skill in the art and are **expressly excluded** by the claims. The Examiner himself, has admitted that "it is known in the art how to make (1) substitutions within an antibody sequence, (2) calculate 70% identity of one sequence to another, and (3) produce a protein that contains one or two CDRs" (Office Action, page 3, lines 14-16).

Moreover, **the Federal Circuit, in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) expressly held that it was not** undue experimentation to screen large numbers of hybridomas for particular desired monoclonal antibodies. As stated by the Court:

> Enablement is not precluded by the necessity of some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. "[T]he key word is 'undue' not 'experimentation'. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In the instant case, Applicants have created an antibody library comprising 7×10^9 members (*see, e.g.,* page 59, line 19). Clearly, Applicants have taught how to make an enormous library. Screening such a library for specific internalizing c-erbB2 antibodies requires at most routine experimentation. Accordingly, the rejection of claims 3-13, 26-22, 34-44, and 53-54 under 35 U.S.C. §112, first paragraph, should be withdrawn.

If it is the Examiner's position that the antibodies recited in claims 3-13, 26-22, 34-44, and 53-54 **would not function** as claimed (*i.e.* that no antibody meeting the limitations of these claims would specifically bind c-erbB2 as recited) then the Examiner should properly make a utility rejection under 35 U.S.C. §101.

Applicants note, however that, under the new Utility Guidelines, to meet the utility requirement, the invention must provide a **specific**, **substantial** and **credible** utility (*see,* Federal Register, 66(4): 1092-1099). In the instant case, the Examiner's concerns would go to "credible utility". Under the Patent Office's own guidelines:

> A rejection based on lack of utility **should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record**. Office personnel are reminded that **they must treat as true a statement of fact made by an applicant in relation to an asserted utility**, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. [emphasis added] (Federal Register, 66(4): 1098-1099)

In the instant case, the Examiner has failed to establish that " that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement" (*i.e.,* that one of ordinary skill in the art would believe that there exist no operable embodiments corresponding to claims).

Thus, for example, claim 8, recites:

> 8. The antibody of claim 1, wherein said antibody comprises at least two complementarity determining region (CDRs) of SEQ ID NO: 1.

This claim does not limit the antibody to two CDRs. Rather, this claim requires that the antibody include two CDRs of SEQ ID NO:1. One of ordinary skill in the art would readily appreciate that antibodies exist and can readily be made that **comprise** at least two CDRs of SEQ ID NO:1 and that specifically bind to c-erbB2 as recited in claim 1 (indeed, such antibodies are illustrated in the specification). Antibodies that do not show such binding specificity are effectively excluded by the claim language. The Examiner has failed to establish that the **claimed invention** would not work. Indeed, the claim scope is exactly commensurate with a specific, substantial and credible utility. The Examiner has thus failed to make a *prima facie* case under 35 U.S.C. §101/§112. Accordingly the rejection should be withdrawn.

35 U.S.C. §103(a).

The rejection of claims 1, 34-38, and 53-54 under 35 U.S.C. §103(a) as allegedly unpatentable over Maier *et al.* (1991) *Cancer Res.*, 51: 5361-5369 taken with Bird *et al.* (1988) *Science,* 242: 423-426 was maintained. According to the Examiner, Maier *et al.* teaches the monoclonal antibody TA1 with is an internalizing antibody that specifically binds to the c-erbB2 receptor. Maier *et al.* does not teach a single chain antibody. Bird *et al.* is cited as teaching a single chain antibody. The Examiner allegedly found motivation in Bird *et al.* to produce the claimed single-chain antibody. Applicants respectfully traverse.

In maintaining his rejection, the Examiner has improperly formulated the §103 rejection. Under Federal Circuit case law, the Examiner must consider the obviousness of the claimed compound in light of the compound(s) identified in the prior art (*i.e.*, **compound must be compared to compound**). It is improper to consider the **method of making** in formulating such a rejection. As stated by the Federal Circuit:

> As stated in The PTO's focus on known methods for potentially isolating the claimed DNA molecules is also misplaced because the claims at issue define compounds, not methods. . . . **We today reaffirm the principle, stated in *Bell*, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.** [emphasis added] *Deuel*, 51 F.3d at 1555.

In the present case, the Examiner has failed to show how the cited references provide any specific information about the **particular claimed** antibodies. The Examiner is reminded that claim 1 expressly recites:

> 1. A **single chain antibody** that specifically binds to a c-erbB2 receptor, **wherein said antibody specifically binds to an epitope bound by F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2)**, and further wherein said antibody is an **internalizing antibody**.

At best, the cited art could be construed as an invitation to prepare a single chain anti-c-erbB2 antibody using phase display methodology. The Examiner's theory that one skilled in the art might be motivated to try to do what Applicants have accomplished amounts to speculation and an impermissible hindsight reconstruction of Applicants' claimed invention.

A general motivation to create an anti-ErbB2 antibody does not necessarily make obvious the specifically-defined antibodies that are subsequently obtained as a result of that search. There is no teaching or suggestion found in Maier *et al.* or Bird *et al.* that would necessarily lead one of skill to an **"antibody specifically binds to an epitope bound by F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2)**" or to an **internalizing antibody**.

Indeed application of the general methods disclosed in Bird *et al.* could reasonably lead one of skill in the art to antibodies that bind to any of a number of epitopes other than those bound by F5 or C1. Similarly application of these general methods could easily lead to antibodies that are not internalizing.

While there may have been a general motivation to prepare a single chain anti-ERbB2 antibody, that does not necessarily make obvious the particular antibodies recited in the presently pending claims. Indeed, "obvious to try" is not the standard under 35 U.S.C. §103. **A general incentive does not make obvious a particular result**. *In re Deuel, supra.*

In summary, the fact that one can conceive a general process in advance for preparing an undefined compound does not mean that a claimed specific compound or family of compounds was precisely envisioned and therefore obvious.

Accordingly the Examiner has failed to make a proper *prima facie* case and the rejection of claims 1, 34-38, and 53-54 under 35 U.S.C. §103(a) should be withdrawn.

Request for a Telephone Interview.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. However, in the Event that the Examiner fails to find the foregoing arguments persuasive, Applicants expressly request a Telephone Conference (Examiner interview) with the Examiner and his Supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN 09/250,056 WITH ENTRY OF THIS AMENDMENT

In the specification.

[No Amendments]

In the claims:

[No Amendments]

APPENDIX B
CLAIMS PENDING IN USSN 09/250,056 WITH ENTRY OF THIS AMENDMENT

1. A single chain antibody that specifically binds to a c-erbB2 receptor, wherein said antibody specifically binds to an epitope bound by F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2), and further wherein said antibody is an internalizing antibody.

3. The antibody of claim 1, wherein said antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 1 having conservative substitutions; and SEQ ID NO: 2 having conservative substitutions.

4. The antibody of claim 1, wherein said antibody shares at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 and wherein said antibody has a binding affinity for c-erbB2 on cells of at least 10 mM.

5. The antibody of claim 1, wherein the amino acid sequence of said antibody differs from the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 by no more than 30 residues.

6. The antibody of claim 1, wherein said antibody comprises a complementarity determining region (CDR) of SEQ ID NO: 1.

7. The antibody of claim 1, wherein said antibody comprises a complementarity determining region (CDR) of SEQ ID NO: 2.

8. The antibody of claim 1, wherein said antibody comprises at least two complementarity determining region (CDRs) of SEQ ID NO: 1.

9. The antibody of claim 1, wherein said antibody comprises at least two complementarity determining regions (CDRs) of SEQ ID NO: 2.

10. The antibody of claim 1, wherein said antibody comprises at least two complementarity determining region (CDRs) selected from the group consisting of the complementarity determining regions of SEQ ID NO: 1, and complementarity determining regions of SEQ ID NO: 2.

11. The antibody of claim 1, wherein said antibody comprises at least three complementarity determining region (CDRs) selected from the group consisting of the complementarity determining regions of SEQ ID NO: 1, and complementarity determining regions of SEQ ID NO: 2.

12. The antibody of claim 11, wherein said antibody comprises three complementarity determining regions of the amino acid sequence of SEQ ID NO: 1.

13. The antibody of claim11, wherein said antibody [has] comprises three complementarity determining regions of the amino acid sequence of SEQ ID NO: 2.

14. (Once amended) The antibody of claim 1, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 1.

15. The antibody of claim 1, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 2.

16. A single chain antibody that specifically binds to a c-erbB2 receptor, said antibody comprising at least 10 contiguous amino acids from the polypeptide sequence as set forth in SEQ ID NO: 1 or SEQ ID NO: 2, wherein said antibody:

when presented as an antigen, elicits the production of an anti-idiotypic antibody that specifically binds to a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 1 or SEQ ID NO: 2; and

does not bind to antisera raised against the polypeptide set forth in SEQ ID NO: 1 and SEQ ID NO: 2, that has been fully immunosorbed with the polypeptides set forth in SEQ ID NO: 1 and in SEQ ID NO: 2.

17. The antibody of claim 16, wherein said antibody shares at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 1or SEQ ID NO: 2 and wherein said antibody has a binding affinity for c-erbB2 on cells of at least 10 mM.

18. The antibody of claim 16, wherein the amino acid sequence of said antibody differs from the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 by no more than 30 residues.

19. The antibody of claim 16, wherein said antibody comprises a complementarity determining region (CDR) of SEQ ID NO: 1.

20. The antibody of claim 16, wherein said antibody comprises a complementarity determining region of SEQ ID NO: 2.

21. The antibody of claim 16, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 1.

22. The antibody of claim 16, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 2.

34. A chimeric molecule that specifically binds a cell bearing a c-erbB-2, said chimeric molecule comprising an effector molecule attached to an antibody of claims 1 or 16.

35. The chimeric molecule of claim 34, wherein said effector is selected from the group consisting of a cytotoxin, a label, a radionuclide, a drug, a liposome, a ligand, and an antibody.

36. The chimeric molecule of claim 34, wherein said chimeric molecule is a fusion protein.

37. The chimeric molecule of claim 34, wherein said cell is a cancer cell.

38. The chimeric molecule of claim 37, wherein said cancer cell is a breast cancer cell.

39. The chimeric molecule of claim 34, wherein said antibody shares at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 1or SEQ ID NO: 2 and wherein said antibody has a binding affinity for c-erbB2 of at least 10 mM.

40. The chimeric molecule of claim 34, wherein the amino acid sequence of said antibody differs from the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 by no more than 30 residues.

41. The chimeric molecule of claim 34, wherein said antibody comprises a complementarity determining region (CDR) of SEQ ID NO: 1.

42. The chimeric molecule of claim 34, wherein said antibody comprises a complementarity determining region (CDR) of SEQ ID NO: 2.

43. The chimeric molecule of claim 34, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 1.

44. The chimeric molecule of claim 34, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 2.

53. A composition comprising a pharmacological excipient and the antibody of claims 1 or 16

54. A composition comprising a pharmacological excipient and the chimeric molecule of claim 34.